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BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

| EXAMINER |
|---|
| STRZELECKA, TERESA E |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1637 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/673,884 | ASADA ET AL. | |
| | Examiner | Art Unit | |
| | Teresa E. Strzelecka | 1637 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *16 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *16,18,31,34,36 and 38-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *16 and 40-42* is/are allowed.

6)☒ Claim(s) *18,31,34,36,38,39 and 43-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. This office action is in response to an amendment filed August 16, 2007. Claims 16, 18, 31, 34, 36 and 38-45 were previously pending. Applicants amended claims 16, 18, 31, 36, 39 and 43. Claims 16, 18, 31, 34, 36 and 38-45 are pending and will be examined.

2. Applicants' amendments overcame the following rejections: rejection of claims 16, 18, 31, 34, 36, 38 and 40-42 under 35 U.S.C. 112, first paragraph, enablement; rejection of claims 16, 18, 40-42 and 45 under 35 U.S.C. 102(a) as anticipated by Al-Saoud et al.; rejection of claim 39 under 35 U.S.C. 103(a) over Demeke et al. and Barnes; rejection of claim 39 under 35 U.S.C. 103(a) over Tasa et al. and Barnes; rejection of claims 43 and 44 under 35 U.S.C. 103(a) over Demeke et al. and Barnes in view of Stratagene Catalog; rejection of claims 43 and 44 under 35 U.S.C. 103(a) over Tasa et al. and Barnes in view of Stratagene Catalog. The provisional double-patenting rejection of claims 16, 18, 31, 36, 39 and 43 over claims 10-17 of the co-pending application 10/435,633 is withdrawn in view of the abandonment of the application.

3. All of the other previously presented rejections are maintained for reasons given in the "Response to Arguments" below. This office action presents new grounds for rejection necessitated by amendment.

### *Response to Arguments*

4. Applicant's arguments filed August 16, 2007 have been fully considered but they are not persuasive.

Regarding the rejection of claims 39 and 43-45 under 35 U.S.C. 112, first paragraph, scope of enablement, Applicants argue that the benefits of dermatan sulfate, polystyrene sulfate and polyvinyl sulfate are disclosed in Example 16, Table 12.

However, analysis of Table 12 shows that while the PCR reaction took place under conditions when dermatan sulfate or polyvinyl sulfate were present in the reaction mixture, there was no "enhancement", according to Applicants' explanation of the symbols. Therefore, the enablement rejection is maintained for claims 39, 43 and 44.

***Claim Rejections - 35 USC § 112 – Scope of Enablement***

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

6. The specification shall contain a written description of the invention, and of the manner and process of making and using it,

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 39, 43 and 44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for sulfated-fucose-containing polysaccharides, sodium alginate, sodium polyglutamate, sodium polyacrylate and κ carrageenan as PCR activators, does not reasonably provide enablement for dextran sulfate, rhamnan sulfate, dermatan sulfate, heparan sulfate, hyaluronic acid, polyglutamic acids, polyacrylic acids, polyvinyl sulfates, polystyrene sulfates or their salts and heparin as PCR activators. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to compositions and kits for performing PCR where heparin or a number of other acidic macromolecular substances is added to enhance PCR. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims encompass the use of dermatan sulfate or polyvinyl sulfates or their salts to enhance PCR. The claims broadly encompass the use of the method on PCR samples derived from any cell type, ranging from plants to animals to soil microorganisms. The method applies to any PCR inhibitor, which can include DNA itself when too much target is present, as well as plant secondary metabolites and, as will be discussed below, the behavior of the other substances in amplification reactions such as PCR has not been evaluated.

Quantity of Experimentation

The quantity of experimentation in this area is large since there is significant variability in the efficacy of steps taken to enhance PCR. This experimentation must take into account variables that depend upon the environment in which the DNA is found as well as the age of the DNA sample and the source of the DNA sample. Different inhibitors are present in ancient DNA samples than in modern DNA samples and different PCR inhibitors are present in plants than are present in blood samples or soil samples. Each of these unique sample types would require independent experimentation and screening in order to determine the efficacy and ability of specific compounds

to enhance PCR. Such efforts are inventive, unpredictable and difficult undertakings, as shown by the many patents such as Harvey et al. (U.S. Patent 6,168,922), which discusses removal of PCR inhibitors. The efficacy of any particular compound to enhance PCR of any particular sample would need to be demonstrated. This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The unpredictability of the art and the state of the prior art

Except for the polysaccharides cited above, Applicants did not show that any other polyionic substances enhance PCR reactions.

Peters (U.S. 2003/0092135) teaches that polyanions themselves are inhibitory to PCR, noting "Acid polyanionic polysaccharides have been characterized as the major PCR inhibitor in plant DNA isolations (Demeke et al., 1992), whereas sulfated polysaccharides, such as dextran sulfate and heparin were identified as potent PCR inhibitors contaminating DNA preparations from blood cells (Al-Soud et al., 2001). Sulfated polysaccharides in particular show a broad spectrum of inhibition against a variety of DNA-modifying enzymes including Polynucleotide Kinase (Wu et al., 1971), restriction endonucleases (Do et al., 1991) and retroviral reverse transcriptases (Moelling et al., 1989). Although the inhibitory effect of polyanions and sulfated polysaccharides in particular has been studied for many years, the exact mechanism is not known (see paragraph 21)."

Therefore, the great weight of both the prior and post filing date art, in both the patent and non-patent literature, teach that addition of polyionic compounds does not reduce inhibition as claimed in this application. The examiner did not find a single prior art patent or non-patent

literature reference that yielded a different conclusion. Therefore, one of ordinary skill in the art would not conclude that any polyionic acidic polymers can be used to enhance PCR amplification.

Working Examples

The specification has no working examples showing enhancement of PCR amplification by the following substances: dextran sulfate, rhamnan sulfate, dermatan sulfate, heparan sulfate, hyaluronic acid, polyglutamic acids, polyacrylic acids, polyvinyl sulfates, polystyrene sulfates or their salts.

Guidance in the Specification.

The specification teaches that acidic macromolecular compounds can be used to enhance amplification, but shows that only the following substances actually do: sulfated-fucose-containing polysaccharides, sodium alginate, sodium polyglutamate, sodium polyacrylate and κ carrageenan.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the level of unpredictability and the teaching of prior art documents that polyanions are PCR inhibitors, support the conclusion of undue experimentation. The specification provides one with little written description or guidance that leads one to overcome the art recognized fact that polyanions are themselves PCR inhibitors. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of any working examples and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would

require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

***Claim Rejections - 35 USC § 103***

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 18 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Demeke et al. (Biotechniques, vol. 12, pp. 332, 334, 1992; cited in the IDS and in a previous office action) and Barnes (U.S. Patent No. 5,436,149 A; cited in a previous office action).

A) Regarding claims 18 and 45, Demeke et al. teach DNA synthesis reaction compositions comprising Taq DNA polymerase and one of the following polysaccharides: carrageenan, pectin and dextran sulfate, together with reaction components necessary for DNA synthesis (Abstract; page 332, second paragraph; Table 1).

B) Demeke et al. do not teach a polymerase having 3'-5' exonuclease activity.

C) Barnes teaches a composition comprising two DNA polymerases, one with 3'-5' exonuclease activity and one without such activity (col. 3, lines 62-67; col. 4, lines 1-11; col. 16, lines 55-61).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used two polymerases with different 3'-5' exonuclease activities of Barnes in the composition of Demeke et al. The motivation to do so, provided by Barnes, would have been that using such polymerase combination allowed amplification of long DNA targets (col. 16, lines 55-61).

10. Claims 18 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tasa et al. (Meth. Mol. Cel. Biol., vol. 5, pp. 122-124, 1995; cited in the IDS and in a previous office action) and Barnes (U.S. Patent No. 5,436,149 A; cited in a previous office action).

A) Tasa et al. teach a DNA synthesis reaction comprising a Taq DNA polymerase and heparin together with reaction components necessary for DNA synthesis (Abstract; page 123, second paragraph and paragraph entitled "Methodology").

B) Tasa et al. do not teach a composition comprising a DNA polymerase with 3'-5' exonuclease activity.

C) Barnes teaches a composition comprising two DNA polymerases, one with 3'-5' exonuclease activity and one without such activity (col. 3, lines 62-67; col. 4, lines 1-11; col. 16, lines 55-61).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used two polymerases with different 3'-5' exonuclease activities of Barnes in the composition of Tasa et al. The motivation to do so, provided by Barnes, would have been that using such polymerase combination allowed amplification of long DNA targets (col. 16, lines 55-61).

11. Claims 31 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Al-Soud et al. (Applied Env. Microbiol., vol. 64, pp. 3748-3753, October 1998; cited in the previous office action), as evidenced by Wikipedia ("Heparan Sulfate", April 21, 2007; cited in the previous office action) and Stratagene catalog (page 39, 1988; cited in a previous office action).

A) Regarding claim 31, Al-Soud et al. teach a composition comprising a DNA polymerase or two DNA polymerases, and components necessary for DNA synthesis using a polymerase, as well as diluted minced pork meat (page 3749, paragraphs 2-5). Al-Soud et al. do not specifically teach heparan sulfate. However, as evidenced by Wikipedia, heparan sulfate is present in all animal

tissues. Therefore, by teaching polymerization reaction with meat solutions Al-Soud et al. inherently teach polymerization in the presence of heparan sulfate.

Regarding claim 34, Al-Soud et al. teach *Thermococcus litoralis*-derived DNA polymerase, *Thermococcus acquaticus*-derived DNA polymerase, Taq DNA polymerase and Pyrococcus-derived (Pwo) polymerase (page 3749, second paragraph; Table 1, 2).

B) Al-Soud et al. teach the reaction composition, but they do not teach kits.

C) Stratagene catalog teaches a motivation to combine reagents into kit format (page 39).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the compositions of Al-Soud al. into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. Thus one need not purchase gram quantitites of 10 different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantitites you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control" (page 39, column 1).

12. Claims 36 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Demeke et al. (Biotechniques, vol. 12, pp. 332, 334, 1992; cited in the IDS and in a previous office action), Barnes (U.S. Patent No. 5,436,149 A; cited in a previous office action), and Stratagene catalog (page 39, 1988; cited in a previous office action).

A) Regarding claims 36 and 38, Demeke et al. teach DNA synthesis reaction compositions comprising Taq DNA polymerase (= thermostable DNA polymerase) and one of the following polysaccharides: carrageenan, pectin and dextran sulfate, together with reaction components necessary for DNA synthesis (Abstract; page 332, second paragraph; Table 1).

B) Demeke et al. do not teach two polymerases, one with polymerase 3'-5' exonuclease activity and one without such activity.

C) Barnes teaches a composition comprising two DNA polymerases, one with 3'-5' exonuclease activity and one without such activity (col. 3, lines 62-67; col. 4, lines 1-11; col. 16, lines 55-61).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used two polymerases with different 3'-5' exonuclease activities of Barnes in the composition of Demeke et al. The motivation to do so, provided by Barnes, would have been that using such polymerase combination allowed amplification of long DNA targets (col. 16, lines 55-61).

D) Demeke et al. and Barnes et al. teach the reaction composition, but they do not teach kits.

C) Stratagene catalog teaches a motivation to combine reagents into kit format (page 39).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the compositions of Demeke et al. and Barnes et al. into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. Thus one need not purchase gram quantities of 10 different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the

unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control" (page 39, column 1).

13. Claims 36 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tasa et al. (Meth. Mol. Cel. Biol., vol. 5, pp. 122-124, 1995; cited in the IDS and in a previous office action), Barnes (U.S. Patent No. 5,436,149 A; cited in a previous office action), and Stratagene catalog (page 39, 1988; cited in a previous office action).

A) Regarding claims 36 and 38, Tasa et al. teach a DNA synthesis reaction comprising a Taq DNA polymerase (= thermostable DNA polymerase) and heparin together with reaction components necessary for DNA synthesis (Abstract; page 123, second paragraph and paragraph entitled "Methodology").

B) Tasa et al. do not teach two polymerases, one with polymerase 3'-5' exonuclease activity and one without such activity.

C) Barnes teaches a composition comprising two DNA polymerases, one with 3'-5' exonuclease activity and one without such activity (col. 3, lines 62-67; col. 4, lines 1-11; col. 16, lines 55-61).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used two polymerases with different 3'-5' exonuclease activities of Barnes in the composition of Tasa et al. The motivation to do so, provided by Barnes, would have been that using such polymerase combination allowed amplification of long DNA targets (col. 16, lines 55-61).

D) Tasa et al. and Barnes et al. teach the reaction composition, but they do not teach kits.

C) Stratagene catalog teaches a motivation to combine reagents into kit format (page 39).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the compositions of Tasa et al. and Barnes et al. into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. Thus one need not purchase gram quantities of 10 different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control" (page 39, column 1).

14. No references were found teaching or suggesting claims 16, 39-44. Claims 16 and 40-42 are allowed. Claims 39, 43 and 44 are rejected for reasons given above.

***Conclusion***

15. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the

THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E. Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Teresa E Strzelecka
Primary Examiner
Art Unit 1637

Teresa Strzelecka
10/29/07